REMARKS

The Office Action has been carefully studied. No claim is allowed. Claims 126-159 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

The presently pending set of claims are now cancelled and replaced with a new set of claims 126-159 which presents the claims in a more organized fashion and avoids the 35 U.S.C. §112 issues raised by the examiner.

Previously pending claims that have been amended and renumbered as new claims are as follows:

> 84 (now 126); 67-69, 71-73, 85 (now 127-133); 63 (now 134 and 135); 97-100 (now 136-139); 74 (now 140); 86 (now 141); 75 (now 148); 93 (now 149); 94-95 (now 150 and 151); 77-79 (now 152-154); 87-88, 90 (now 155-157); and 80-81 (now 158-159).

Previously pending claims that are now cancelled and not replaced with new claims are claims 58-62, 64-66, 70, 76, 82, 89, 91-92, and 101-125.

For the examiner's convenience in reviewing the new set of claims 126-159, the following layout summarizes the way the new claims are organized.

Claims 126-133 are directed to pharmaceutical compositions comprising corroles. As stated in the

specification, page 6, last paragraph, corroles have not been disclosed before for any pharmaceutical use and applicants are thus entitled to a broad pharmaceutical composition claim.

Claims 134-154 are directed to a method for inhibiting growth factor receptor tyrosine kinase activity which comprises administering a tetrapyrrolic macrocycle selected from the group consisting of (a) a 5,10,15,20-tetraaryl-porphyrin with some provisos, and (b) a 5,10,15-triaryl-corrole, wherein:

Claims 135-140 are directed to the method using porphyrins;

Claims 141-148 are directed to the method using corroles;

Claim 149 is directed to the method using the growth factor receptor tyrosine kinase;

Claim 150 is directed to the method by the disease or disorder to be treated; and

Claims 151-154 are directed to the method by some of the diseases or disorders and specific compounds useful therein.

Claim 155 is an independent claim directed to a method for inhibiting angiogenesis which comprises administering a 5,10,15,20-tetraaryl-porphyrin or a 5,10,15-triaryl-corrole.

Claim 156 is an independent claim directed to a method for prevention of restenosis after percutaneous transluminal

coronary angioplasty comprising administering a 5,10,15,20-tetraaryl-porphyrin or a 5,10,15-triaryl-corrole.

Claim 157 is an independent claim directed to a method for inhibition of vascular smooth muscle cell proliferation in disorders selected from the group consisting of atherosclerosis, hyperthrophic heart failure and postsurgical restenosis, comprising administering a 5,10,15,20-tetraaryl-porphyrin or a 5,10,15-triaryl-corrole.

Claims 158-159 are directed to new porphyrins.

The examiner asserts that inhibition of growth factor receptor tyrosine kinase (GFRTK) activity is not a real world utility but is a laboratory utility and requires election of a specific real world disease. The examiner indicates that examination of one method cannot begin until that one method is elected. While the examiner acknowledges that the instant application is a 371 application, the examiner holds that 37 CFR 1.475 makes it clear that applicants are entitled to have one specific use of their compounds examined in the application.

Merely in order to be responsive to the requirement for the election of a specific real world disease, applicants provisionally elect post-surgical restenosis with traverse.

While it is true that 37 CFR 1.475 provides for examination of only one specific use (method) claim, it is

emphasized that this does not apply to the compound claims themselves, which cannot be limited to a specific use. Furthermore, as the instant application is a 371 application, PCT Unity of Invention controls and the issue with regard to the use/method claims is whether or not the utilities share a special technical feature. It is clear that the special feature shared by all the present claims is the inhibition of growth factor receptor tyrosine kinase (GFRTK). This is what all the utilities, such as inhibiting angiogenesis, preventing restenosis, etc., have in common. Thus, the property of inhibiting GFRTK is a special technical feature which permits all the uses/methods to be claimed and examined together in the same application.

Regarding the issue of whether or not the inhibition of GFRTK or even the inhibition of angiogenesis, which results from inhibition of GFRTK, is a real world utility, the "Background of the Invention" section of the specification discloses that it is well known that there are many *in vivo* uses for inhibiting growth factor receptor tyrosine kinase. For instance, fibroblast growth factor receptors (FGFR), which are growth factor receptor tyrosine kinases, were found to play a role in genetically acquired growth disorders. The present specification discloses in the paragraph bridging pages 2 and 3 that:

> Naski et al., 1996, have demonstrated that both the achondroplasia and thanatophoric dysplasia mutations constitutively activate the receptor as evidenced by receptor tyrosine phosphorylation. These findings have been biologically supported by knock out of the FGFR-3 gene (Deng et al., 1996). Furthermore, it seems that FGFRs are involved in bone and cartilage benign tumors, such as hereditary multiple exotosis, osteoarthritis and others.

Vascular endothelial growth factor (VEGF) is disclosed in the full paragraphs of page 3 as being a multifunctional cytokine that exerts a key role in physiological and pathological neoangiogenesis by stimulating endothelial cell proliferation and vessel hyperpermeability and plays a major role in the pathogenesis of many diseases including hypervascularized tumors, rheumatoid arthritis, cutaneous diseases and proliferative retinopathies. It is further disclosed on page 3, lines 23-29 that:

> Current evidence (Patt et al., 1998) suggests that hypoxia is also the driving force for VEGF gene expression in cells *in vivo* and represents the most important trigger for tumor angiogenesis and edema. Recent approaches to inhibit tumor angiogenesis and metastasis formation concentrate on the disruption of VEGF/VEGF receptor signal transduction pathway *in vivo*. Persistent angiogenesis may cause or exacerbate certain diseases such as psoriasis, rheumatoid arthritis, hemangiomas, angiofibromas, diabetic retinopathy and neovascular glaucoma.

In addition, the specification on page 6, lines 19-27, discloses that some porphyrin derivatives have been reported for use in combination with electromagnetic radiation and radioactive emissions for inhibiting angiogenesis, citing WO 95/24930, WO 94,12239, WO 93/02192 and U.S. Patents 5,576,013 and 5,284,647. Clearly, the inhibition of angiogenesis is an important real world utility that is instantly recognized by those in the art.

The specification continues to disclose other uses for inhibiting growth factor receptor tyrosine kinases such as PDGF receptors, hepatocyte growth factor (HGF) receptors and nerve growth factor receptors.

In view of the wealth of information on the many uses of inhibiting growth factor receptor tyrosine kinases, it is clear that those of skill in the art would consider the inhibition of growth factor receptor tyrosine kinases to be a specific, credible and substantial utility in compliance with 35 U.S.C. §101.

Reconsideration and withdrawal of the restriction requirement and the examiner's holding of non-compliance with 35 U.S.C. §101 and §112, first paragraph, are therefore respectfully requested.

The previously pending claims have been rejected under 35 U.S.C. 112, first and second paragraphs for lack of clarity

and inadequate support with respect to the term heteroaryl. The examiner asserts, *inter alia*, that "one, on reading heteroaryl, has no idea whether the ring is monocyclic or more. What the heteroatoms are, or where they are located in what size ring." The examiner further asks "what is intended by aryl or heteroaryl?" and states that "the support in the specification is inadequate for the breadth claimed. Heteroaryl is a huge area of chemistry, that completely overshadows the formula I. The heteroaryl term is not set forth in clear, specific language. The reader must produce the heterocyclic ring in question".

The specific definitions of aryl and heteroaryl and their substitutions as supported in the specification are now recited in the new set of claims and therefore, the present claims avoid the rejections under 35 U.S.C. §112 as set forth on pages 3-8 of the Office Action.

The examiner requests clarification of the purpose of the *provisos* in previously pending claim 63, now presented as new claims 134 and 135. Applicants clarify that the provisos that at least two of the aryl groups in both the porphyrin and the corrole compounds have to be positively charged have been introduced as a condition for their activity and not because of prior art.

The provisos for the porphyrin compounds in previously pending claims 63 and 80 (now presented as new claims 134-135 and 158) were introduced in order to overcome the prior art (documents D1: WO 98 33503 and D8: FR 2,656,866) cited by the examiner in the previous Office Action, Paper No. 10. These provisos provide that the porphyrin compounds encompassed by the invention will always have at least one tetrafluorophenyl or pentafluorophenyl radical. These radicals have not been disclosed or suggested by D1 or D8.

Claim 78, now presented as new claim 153, has been rejected under 35 U.S.C. §112, first and second paragraphs, because the examiner holds that the treatment of all primary tumors and metastases is extremely unlikely. This rejection is respectfully traversed.

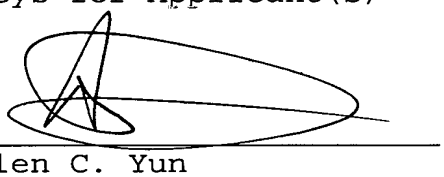
It is emphasized that it is not applicants' intent to cure all primary tumors but rather, by inhibiting growth factor receptor tyrosine kinase, the cell proliferation of primary tumors and metastases is inhibited. As it is known that all tumors and metastases are mediated to some extent by growth factors, it is certainly not incredible that inhibition of growth factors would cause inhibition of primary tumors and metastases.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By 
Allen C. Yun
Registration No. 37,971

ACY:pp
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\B\BENA\Yayon4\Pto\amd 05-23-03.doc